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L3: Entry 31 of 39 File: USPT Feb 3, 1998

DOCUMENT-IDENTIFIER: US 5714374 A
TITLE: Chimeric rhinoviruses

Brief Summary Text (5):
To overcome some of these complications, considerable research effort has been expended to examine the feasibility and efficacy of immunizing with empty viral capsids and pathogen-derived proteins and peptides. Unfortunately, the antigenicity profiles for complex virions and empty capsids are often quite different. This phenomenon has been documented for several picornaviruses, including rhinovirus (Lonberg-Holm & Yin, J. Virol., 12:114-123, 1973), poliovirus (Mayer, et al., J. Immunol., 78:435-455, 1957), foot-and-mouth disease virus (FMDV) (Rowlands, et al., J. Gen. Virol., 26:227-238, 1975), and Coxsackie B virus (Frommhagen, J. Immunol., 95:818-822, 1965). Studies with individual virion proteins have shortcomings as well. Individual coat proteins, for instance, have antigenic determinants absent from intact viruses (Wiegers & Derrick, J. Gen. Virol., 64:777-785, 1983) and are generally far less effective at stimulating neutralizing antibodies than are whole virions. Attempts to use peptides to provide protection against dangerous pathogens have also been disappointing. Despite occasional examples of success (e.g., Bittle, et al., Nature, 298:30-33, 1982; Pfaff, et al., EMBO. J., 1:869-874, 1982), most peptides fail to protect vaccinated animals, even when they are capable of stimulating the production of neutralizing antibodies (e.g., Ada & Skehel, Nature, 316:764-765,1985; Tiollais, et al., Nature, 317:489-495, 1985; DiMarchi, et al., Science, 232:639-641, 1986).

Detailed Description Text (11):
The cellular immune response also plays an extremely important role in providing immunity against viruses and other pathogens. Among the components of cell-mediated immune (CMI) response are cytotoxic T-lymphocytes (CTLs), macrophages, and so forth. Chimeric rhinoviruses will also stimulate the cellular immune system in relevant ways that will be beneficial in providing immunity against foreign pathogens. The determinants for optimal stimulation of cellular immunity are less well characterized than for those of the humoral immune response. It is anticipated that T-cell epitopes of foreign pathogens (and other sequences that provoke CMI) can be successfully placed in many portions of the HRV coat proteins in addition to the surface exposed regions. For this purpose, epitopes that provoke CMI can also be inserted into any of the non-structural proteins of the chimeric HRV, such as the polymerase (3D protein) or protease (3C protein) that are also produced in high copy number during infection in the host.

Detailed Description Text (17):
The recombinant chimeric human rhinoviruses have potential uses as vaccines for diseases and disorders wherein the source of the chimeric region is derived from a viral, neoplastic, parasitic, or bacterial source. Numerous viral-specific antigens are known to those of skill in the art and can potentially be incorporated into the chimeric rhinoviral vaccines of the invention. For example, such antigens, or portions thereof, which encode the epitope(s) include such sources as influenza A hemagglutinin; hepatitis A virus VP1 and VP3; hepatitis B surface, core, or E antigens; poliovirus capsid protein VP1, VP2, and VP3; rabies virus glycoprotein; retroviral envelope glycoproteins or capsid proteins; foot and mouth disease virus VP1; herpes simplex virus glycoprotein D; Epstein-Barr virus glycoprotein; pseudorabies virus glycoproteins; vesicular stomatitis virus glycoprotein, to name a few. Bacterial antigens that can be incorporated include those from the genera Pneumococcus, Salmonella, Shigella, Clostridia, Pseudomonas, Streptococcus,

Staphylococcus, and Neisseria, to name a few. Parasitic antigens that can be presented on the chimeric rhinoviruses include those from the genera Trypanosoma, Leishmania, Plasmodium, and Toxoplasma, to name a few. Neoplastic antigens that can be displayed on the chimeric rhinoviruses include those from tumors and carcinomas (e.g., mammary, colon) and those from oncogene products or mutated oncogene products (e.g., ras, myc).

Detailed Description Paragraph Table (1):
TABLE 1

CANDIDATE SURFACE-EXPOSED HRV14 REGIONS FOR PLACEMENT OF CHIMERIC REGIONS LOCATIONS OF RESIDUES	RESIDUES REPLACED	ESCAPE MUTATIONS IN REGION	LARGE	INTERMEDIATE	SMALL
I. NIm sites A. NIm-IA	1091,1095	1082-1099	1082-1099	1085-1096	1091-1095
B. NIm-IB	1083,1085	1079-1089	1079-1089	1081-1087	1082-1086
1138,1139	1134-1143	1134-1143	1135-1141	1136-1140	
C. NIm-II	2158,2159,2161,216	2155-2169	2155-2169	2157-2165	2158-2162
2	2132-2140	--	2132-2140	2134-2138	2136
1206-1214	--	1206-1214	1208-1212	1210	
D. NIm-III	3072,3075,3078	3068-3082	3068-3082	3070-3080	3072-3078
3203	3199-3207	--	3199-3207	3201-3205	1287
1283-1289	--	1283-1288	1284-1288	II. Other surface regions	
A. VP3 "knob"	--	3053-3069	3053-3069	3057-3065	3058-3062
B. FMDV loop	--	1200-1221	1200-1221	1206-1214	1208-1212
C. VP2 BC	--	2070-2078	--	2070-2078	2072-2076
loop					
D. VP1 C-	--	1255-1289	1255-1289	1265-1280	1270-1275
terminus					
E. VP2 C-	--	2254-2262	--	2254-2262	2258-2262
terminus					
F. VP3 C-	--	3222-3236	--	3227-3236	3230-3236
terminus					

Other Reference Publication (14):
Bittle, et al., "Protection against foot-and-mouth disease by immunization with a chemically synthesized peptide predicted from the viral nucleotide sequence," Nature, vol. 298, pp. 30-33, 1982.

Other Reference Publication (22):
DiMarchi, et al., "Protection of Cattle Against Foot-and-Mouth Disease by a Synthetic Peptide," Science, vol. 232 pp. 639-641, 1986.

Other Reference Publication (61):
Pfaff, et al., "Antibodies against a preselected peptide recognize and neutralize foot and mouth disease virus," EMBO. J., vol. 1, pp. 869-874, 1982.

Other Reference Publication (68):
Rowlands, et al., "A Comparative Chemical and Serological Study of the Full and Empty Particles of Foot-and-Mouth Disease Virus," J. Gen. Virol., vol. 26, pp. 227-238, 1975.

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L3: Entry 25 of 39 File: USPT Nov 16, 1999

DOCUMENT-IDENTIFIER: US 5985610 A
TITLE: Self-assembling recombinant papillomavirus capsid proteins

Brief Summary Text (5):
First, it has not been possible to generate in vitro the large stocks of infectious virus required to determine the structural and immunogenic features of papillomavirus that are fundamental to the development of effective vaccines. Cultured cells express papillomavirus oncoproteins and other non-structural proteins and these have been extensively studied in vitro; but expression of the structural viral proteins, L1 and L2 (and the subsequent assembly of infectious virus) occurs only in terminally differentiated layers of infected epithelial tissues. Therefore, the characterization of viral genes, proteins, and structure has necessarily been assembled from studies of virus harvested from papillomas. In particular, papillomavirus structure and related immunity have been carried out in the bovine papillomavirus system because large amounts of infectious virus particles can be isolated from bovine papillomavirus (BPV) warts.

Brief Summary Text (12):
Ghim et al., (1992) reported that when L1 from HPV1, a non-genital virus type associated mainly with warts on the hands and feet, was expressed in mammalian cells, the L1 protein contained conformational epitopes found on intact virions. Ghim did not determine if particles were produced, nor was it evaluated if the L1 protein might induce neutralizing antibodies. Even more recently, Hagansee, et al. (1993) reported that when L1 from HPV1 was expressed in human cells, it self-assembled into virus-like particles. No neutralizing antibody studies were performed.

Other Reference Publication (121):
D.J. Rowlands, et al., A Cmparative Chemical and Serological Study of the Full and Empty Particles of Foot-and-Mouth Disease Virus, J. Gen. Virology, (1975), 26, 227-238.